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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/788,466	03/01/2004	Steven Louis Shafer	44893-0004	9229

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EXAMINER	
ALSTRUM ACEVEDO, JAMES HENRY	
ART UNIT	**PAPER NUMBER**
1616	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/788,466	SHAFER ET AL.	
	Examiner	Art Unit	
	James H. Alstrum-Acevedo	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-48* is/are rejected.

7)☒ Claim(s) *39* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 29-48 are pending. Applicants previously cancelled claims 1-16. Applicants have newly cancelled claims 17-28. Applicants have amended claim 48. Claims 37-47 were withdrawn from consideration as being drawn to a non-elected invention, but have been rejoined. **All pending claims are under consideration in the instant office action.** Receipt and consideration of Applicants' amended claim set and remarks/arguments submitted on September 5, 2007 are acknowledged.

Moot Rejections/objections

All rejections and/or objections of claims 17-28 cited in the previous office action mailed on April 5, 2007 **are moot**, because said claims have been cancelled.

Election/Restrictions

Upon reconsideration, claims 37-47 are rejoined to the instant application.

Specification

Claim 39 is objected to because of the following informalities: the word "each" is misspelled as "each" on line 9 of said claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claim 48 under 35 U.S.C. 112, first paragraph (scope of enablement) cited on pages 3-6 of the office action mailed on April 5, 2007 **is withdrawn**, per Applicants' claim amendments limiting the claimed opioid formulation to a formulation comprising (a) a rapid onset-opioid selected from the group consisting of remifantanil, alfentanil, sufentanil, or fentanyl and (b) a slow onset-opioid selected form the group consisting of methadone or morphine, wherein the combination of (a) and (b) provides a peak concentration at an effect site as described in instant claim 48.

Response to Arguments

Applicant's arguments, see page 10, filed 9/5/07, with respect to the rejection of claim 48 under 35 U.S.C. 112, first paragraph (scope of enablement) have been fully considered and are persuasive. The rejection of claim 48 under 35 U.S.C. 112, first paragraph (scope of enablement) has been withdrawn.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

The rejection of claim 48 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention **is withdrawn** per Applicants' claim amendments removing indefinite language.

Response to Arguments

Applicant's arguments, see page 10, filed 9/5/07, with respect to the rejection of claim 48 under 35 U.S.C. 112, second paragraph have been fully considered and are persuasive. The rejection of claim 48 under 35 U.S.C. 112, second paragraph has been withdrawn.

Claims 37-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an opioid formulation comprising either (1) fentanyl and liposomally encapsulated fentanyl or (2) the combination of (a) remifantanil, alfentanil, sufentanil, or fentanyl and (b) methadone, wherein said formulation induces analgesia before the onset of side effects and/or toxicity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. An analysis based upon the Wands factors is set forth below.

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In *Genentech Inc. v. Novo Nordisk* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993),. See also *Amgen Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); *In re Fisher* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Further, in *In re Wands* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman (230 USPQ 546, 547 (Bd Pat App Int 1986)). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence

of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Breadth of Claims/ Nature of the invention

Applicants' claims are broad, because these claim the mixture of one or more rapid onset opioids in combination with any excipient, wherein claims 37-38 require that the mixture of one or more rapid-onset opioids induce analgesia before the onset of side effects and/or toxicity.

State of the Prior Art

The pharmacokinetic profile of liposome-encapsulated fentanyl is known in the prior art (Hung, O. R. et al. "Pharmacokinetics of Inhaled Liposome Encapsulated Fentanyl," *Anesthesiology*, **1995**, *83(2)*, 277-284). It is known in the art that one can increase the encapsulation efficiency of fentanyl merely by changing the amount of soy phospholipid used to make the liposomes (Tan, S. et al. "Sustained Tissue Drug Concentrations Following Inhalation of Liposome-Encapsulated Fentanyl in Rabbits," *Drug Delivery*, **1996**, *3(4)*, pp 252, left column). Thus, the ratio of free fentanyl to liposomally encapsulated fentanyl is an optimizable parameter. It is known in the prior art that opioids (e.g. fentanyl) can be toxic, result in serious side effects, and/or be lethal if given in inappropriate concentrations (instant specification, [0087]-[0088]; Drug Information Handbook, Lexi-Comp, Inc.: Hudson, OH, 1999-2000, pp 37-39, 414-416, 651-652, and 1099-1100). It is well known that opioid response is highly individualized (instant specification, [0087]). It is also noted that post-filing art indicates that opiate medication and the onset of analgesia versus the onset of dangerous and toxic side effects can be difficult to predict for a single opiate, let alone for a combination of any two opiates

(Lötsch, J., "Pharmacokinetic-Pharmacodynamic Modeling of Opioids," *Journal of Pain and Symptom Management*, **May 2005**, *29 (5S)*, pp S90-S103).

Level of One of Ordinary Skill & Predictability/Unpredictability in the Art

The level of a person of ordinary skill in the art is high, with ordinary artisans having advanced medical and/or scientific degrees (e.g. M.D., Ph.D., Pharm. D. or combinations thereof). There is a general lack of predictability in the pharmaceutical art. *In re Fisher*, 427, F. 2d 833, 166, USPQ 18 (CCPA 1970).

Guidance/Working Examples

Applicants have provided guidance in the specification in the form of working examples, figures, and computer-simulated pharmacokinetic profile models based on the STELLA® computer language. Said guidance is limited to pulmonary formulations comprising the combination of (1) a rapid onset opioid and (2) a slow onset opioid. Applicants have provided no guidance regarding the combination of two rapid onset opioids or two slow onset opioids. Furthermore, given Applicants' disclosure that their invented formulations specifically require the combination of (1) a rapid onset opioid and (2) a slow onset opioid, one must conclude that Applicants are not enabled methods administering formulations comprising one or more rapid-onset opioids in a pulmonary formulation that induces analgesia before the onset of side effects and/or toxicity. Thus, Applicants' specification is only enabling for an opioid formulation comprising either (1) fentanyl and liposomally encapsulated fentanyl or (2) the combination of (a) remifantanil, alfentanil, sufentanil, or fentanyl and (b) methadone, wherein said formulation induces analgesia before the onset of side effects and/or toxicity.

Claims 38-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The following claims utilize "means + function" claim language and are deemed to invoke the provisions of 35 U.S.C. §112, 6th paragraph, however, because the specification does not adequately identify the recited means, the following claims and claims dependent therefrom are indefinite: (i) means for forming the formulation into particles...(claims 38- 39); (ii) means for dispensing said formulation (claims 38-39 and 44); and (iii) delivery rate controlling means for limiting the rate...(claim 40)

Claim 28 is vague and indefinite, because said claim depends from a cancelled claim.

Claim 39 is unclear, because it is unclear what are the other types of opioid referred to in lines 9-10 of said claim. The only "type" of opioid recited earlier in claim 44 is a rapid-onset opioid.

Claim 44 is unclear, because it is unclear what are the other types of opioid referred to in line 9 of said claim. The only "type" of opioid recited earlier in claim 44 is a rapid-onset opioid.

Claims 46-47 are vague and indefinite, because said claims depend from a cancelled claim.

Claims 46-47 provide for the use of a formulation according to claim 1, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

The remaining claims are rejected as depending from a rejected claim.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 46-47 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claims 29-36 and 48 under 35 U.S.C. 103(a) as being unpatentable over Mezei et al. (U.S. Patent No. 5451408) **is withdrawn** per Applicants' claim amendments and persuasive arguments.

Response to Arguments

Applicant's arguments, see page 11, filed 9/5/07, with respect to the rejection of claims 29-36 and 48 under 35 U.S.C. 103(a) as being unpatentable over Mezei et al. (U.S. Patent No. 5,451,408) have been fully considered and are persuasive. The rejection of claims 29-36 and 48 under 35 U.S.C. 103(a) as being unpatentable over Mezei et al. (U.S. Patent No. 5,451,408) has been withdrawn.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states, "whoever invents or discovers any new and useful process ... may obtain a patent therefor..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 29 and 48 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 10 and 56 of copending Application No. 10/927,145 (copending '145). This is a provisional double patenting rejection since the conflicting claims have not in fact been patented. The cited claims of the instant application and copending '145 are semantically verbatim.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 29-30, 33-37, 39, 41, and 44-45 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 11, 13-14, 28-33, and 46 of copending Application No. 10/927,145 (copending '145) for the reasons of record set forth on page 9 of the office action mailed on July 15, 2006 and because Applicants have requested that the instant rejection be held in abeyance. Regarding the rejection of the newly rejoined claims, these recite concentrations of specific opioids that are readily obtainable via routine optimization by an ordinary skilled artisan. The device claims in both the instant application and copending '145 recite similar means + function claim language and contain a substantially similar formulation within the respectively claimed devices.

Response to Arguments

Applicants have requested that the instant rejection be held in abeyance until the claims of the instant application or those of copending '466 are in condition for allowance. Neither application is in condition for allowance at this time, thus the instant rejection is maintained.

Conclusion

Claims 29-48 are rejected. Claim 39 is objected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner can normally be reached on M-F, 9:00-6:30, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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